UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,658	12/04/2000	Jonathan Zonana	6005-55924	3101

7590 02/08/2006

KLARQUIST SPARKMAN CAMPBELL LEIGH & WHINSTON, LLP
One World Trade Center
Suite 1600
121 S.W. Salmon Street
Portland, OR 97204

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,658	ZONANA ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/14/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,23-26,60-63,65-68 and 72-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,23-26,60-63,65-68 and 72-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *9/8/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 11/14/05. Claims 5-22, 27-59, 64 and 69-71 have been cancelled. Claims 1, 2, 4, 23-26, 60-63, 65-68 and 72-77 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Claim Objections

Claim 24 and 25 recite that the protein "encodes" a polypeptide. However, proteins cannot encode other polypeptides.

Claim 72 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Both claims recite a method of increasing hair follicle development by administration of at least 153 amino acids of SEQ ID NO:2.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 22-26, 41-42, 59-69 and 72-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing hair follicle or sweat gland development in newborn Tabby mice suffering from XLHED or HED using an EDA1-II fragment comprising amino acids 239-391, does not reasonably provide enablement for an increase of hair follicle or sweat gland in any subject suffering from XLHED or HED using any EDA1-II fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 5/19/04, 2/4/05 and 7/29/05 and restated below. The rejection has been reworded based upon applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a method of increasing hair follicle, tooth or sweat gland development by increasing EDA1-II activity.

2) **Scope of the invention**. The claims recite that EDA1-II protein activity can be increased by administration of EDA1-II protein to humans suffering from ectodermal disease. Therefore the instant invention uses methods of protein therapeutics.

3) **Number of working examples and guidance**. Applicants teach that X-linked hypohidrotic ectodermal dysplasia (HED) is a human genetic disorder characterized by lack of hair, sweat glands and tooth development. The EDA1 gene was identified in adult sweat glands. Tabby mice carry a mutant Tabby gene (Ta) and are characterized by an absence of sweat glands and with anhidrosis and have abnormally shaped teeth. The instant invention is drawn to the identification of an EDA1 splice form EDA1-II that is 94% homologous to the Ta cDNA. Nearly all of the mutations associated with HED are located in the exons coding for this isoform. Based upon this, applicants have proposed assays that are designed to identify agents that enhance EDA1-II activity (page 7, line 32- page 8, line 22). These include *in vivo* methods that involve intradermal injection or topical application of the protein to the skin or tails of newborn tabby mice and detection of the induction of hair growth and injection of proteins into footpads of newborn tabby mice and monitoring of sweat gland development. *In vitro* assays include application of protein to dissected skin from mouse embryos and calculation of hair follicles that follow as well as application of truncated protein to an *in vitro* tooth organ culture system.

Once proteins that enhance EDA1-II activity have been identified, it is taught that the protein can be used in therapeutic applications. Specifically, it is disclosed that purified protein at concentrations ranging from 1 ng/ml to 1 g/ml (a range of 1,000,000) is applied to the tails, bellies and areas behind the ears of newborn tabby mice, wild type mice and nude mice (see page 50, line 21-37) or is injected into footpads of newborn tabby mice (page 51, line 13-24). These

methods are said to be extrapolated to humans as well as to application of the protein to *in vitro* tooth cultures and the teeth introduced into humans or other organism (see page 51, line 1-12).

While the specification does not provide an actual reduction to practice of these disclosed methods, post filing results are provided which demonstrate intraperitoneal administration of 10-20 μg of purified 239-391 fragment of human EDA to newborn tabby mice.

4) **State of Art**. The state of art for treatment of humans suffering from ectodermal dysplasia is not currently a high art. Cosmetic or functional correction is the only recourse patients have against this disease (see e.g. MedlinePlus medical encyclopedia). However, methods based on protein therapeutics for treatment of ectodermal dysplasia is a high art.

Torchilin and Lukyanov teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260).

Recently, permanent correction of ectodermal dysplasia in tabby mice has been reported (see Gaide and Schneider). In this study, application of EDA1 was conducted in pregnant tabby mice by serial intravenous injections of 400 μg of recombinant EDA1 (in 2mg/ml PBS) following two different dose schedules. Newborn mice received a single intradermal injection at the same dose (see Gaide and Schneider, bridging paragraph page 617-618). Formation of hair, teeth and sweat glands were induced in the newborn mice.

5) **Unpredictability of the art**. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice

experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies.

Furthermore, any successes in the published document by Gaide and Schneider cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of the reference. Considered in closer detail, the teachings of the instant invention differ dramatically from that of Gaide and Schneider. Gaide and Schneider teach administration of recombinant EDA1-II and the Fc domain of IgG1 that is intravenously injected into pregnant Tabby mice intraperitoneally or intravenously into newborn mice for the sole purpose of altering the phenotype of the fetal mice. None of the treatments were successful in altering any of the Tabby phenotypes in the adult mice. Injections at gestational day 11, 13 and 15 at 400 um per injection, called E11 reversed most of the Tabby characteristics except teeth and hair growth were not completely wild type. Other treatments included gestational treatment at day 15 and 17 (E15) as well as injection of newborn mice at day 2, 3, 5, 9 (D2, D3, D5, D9). The subsequent treatments had decreasing effects on the Tabby phenotype. Newborn injections only consistently corrected sweat gland development. However, teeth and hair were either not or were poorly corrected (see e.g. table 1). Applicants have not proposed injection of pregnant Tabby mice with a recombinant EDA1-II that has been engineered to pass the placental barrier. Furthermore, applicants have not indicated that the EDA1-II would be used to reverse phenotype via genetic

routes. Rather the instant specification has indicated that the effects of EDA1-II would be demonstrated in the actual patient injected. Following this approach, the success of treatment in increasing hair follicle, tooth and sweat gland development would be expected to be insufficient in treating each of these disorders as demonstrated by the increasing failure of treatments to reverse the ectodermal phenotype in the newborn mice s demonstrated by Gaide and Schneider. Therefore, means of administration of protein for the treatment of each of these disorders using the guidance provided in the specification is highly unpredictable.

Problems with protein therapeutics identified in the art are not addressed by the methods of the instant invention nor the prior art. Therefore, neither the specification nor art teach one how to treat ectodermal dysplasia by introduction of EDA1-II as neither the specification nor the prior art provide dosages of EDA1-II to administer to patients, schedule of treatments, specific modes of administration of EDA1-II to humans suffering from ectodermal disease is provided.

6) **Summary**. The invention recites a method of treating ectodermal disease by the administration of EDA1-II protein to a subject using gene therapy. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the

skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on page 6 of the amendment filed 11/14/05. Applicant argues that the amendments have clarified that the methods is a method of increasing hair follicle development, sweat gland development or both in a subject having XLHED or HED by administration of at least 153 amino acids of SEQ ID NO:2.

Applicants' arguments made11/14/05 have been considered but are not persuasive. As well, the claims have been evaluated in light of the amendments to the claims but have not been found allowable. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). First, applicants have only demonstrated that in **newborn** and fetal Tabby mice, a protein fragment of EDA1-II comprising amino acids 239-391 is able to induce hair formation and sweat gland development. However, applicants' claims are drawn to the ability to induce hair follicle, sweat gland or both in any subject suffering from XLHED or HED. No treatments were successful in altering any of the Tabby phenotypes in adult mice. While it could be argued that Tabby mice are the acceptable models of ectodermal dysplasia, it is not clear that newborn or fetal Tabby mice serve as a model for subjects of any

age. Furthermore, lack of success in adult mice suggests that the predictability of success is highly unpredictable. Secondly, applicants' claims are drawn to a broad genus of fragments comprising at least 153 amino acids of SEQ ID NO:2. SEQ ID NO:2 is an amino acid of 391 amino acids encoding a splice variant of a gene associated with ectodermal dysplasia called EDA1-II. However, applicants have only demonstrated operability of a single fragment of EDA1-II comprising amino acids 239-391. Hence, the predictability of any fragment comprising 153 amino acids would provide the same function absent a detailed structural/functional relationship of the required amino acids. Therefore, it would require undue experimentation to determine what proteins are active in humans to induce hair follicle or sweat gland development as only a single species of proteins has been identified that is capable of mediating hair follicle and sweat gland development in newborn and fetal Tabby mice.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

February 3, 2006

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER